<https://helda.helsinki.fi>

COSCA (Core Outcome Set for Cardiac Arrest) in Adults : An Advisory Statement From the International Liaison Committee on Resuscitation

COSCA collaborators

2018-06

COSCA collaborators , Haywood , K & Castren , M 2018 , ' COSCA (Core Outcome Set for Cardiac Arrest) in Adults : An Advisory Statement From the International Liaison Committee on Resuscitation ' , Resuscitation , vol. 127 , pp. 147-163 . <https://doi.org/10.1016/j.resuscitation.2018.03.022>

<http://hdl.handle.net/10138/302273>

<https://doi.org/10.1016/j.resuscitation.2018.03.022>

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

ILCOR Advisory Statement

COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation[☆]

Kirstie Haywood¹, Laura Whitehead¹, Vinay M. Nadkarni, Felix Achana, Stefanie Beesems, Bernd W. Böttiger, Anne Brooks, Maaret Castrén, Marcus E.H. Ong, Mary Fran Hazinski, Rudolph W. Koster, Gisela Lilja, John Long, Koenraad G. Monsieurs, Peter T. Morley, Laurie Morrison, Graham Nichol, Valentino Oriolo, Gustavo Saposnik, Michael Smyth, Ken Spearpoint, Barry Williams, Gavin D. Perkins, On behalf of the COSCA Collaborators

ARTICLE INFO

Keywords:

AHA Scientific Statements
Cardiac arrest
Consensus
Quality of life
Treatment outcome

ABSTRACT

Cardiac arrest effectiveness trials have traditionally reported outcomes that focus on survival. A lack of consistency in outcome reporting between trials limits the opportunities to pool results for meta-analysis. The COSCA initiative (Core Outcome Set for Cardiac Arrest), a partnership between patients, their partners, clinicians, research scientists, and the International Liaison Committee on Resuscitation, sought to develop a consensus core outcome set for cardiac arrest for effectiveness trials. Core outcome sets are primarily intended for large, randomised clinical effectiveness trials (sometimes referred to as *pragmatic trials* or *phase III/IV trials*) rather than for pilot or efficacy studies. A systematic review of the literature combined with qualitative interviews among cardiac arrest survivors was used to generate a list of potential outcome domains. This list was prioritised through a Delphi process, which involved clinicians, patients, and their relatives/partners. An international advisory panel narrowed these down to 3 core domains by debate that led to consensus. The writing group refined recommendations for when these outcomes should be measured and further characterised relevant measurement tools. Consensus emerged that a core outcome set for reporting on effectiveness studies of cardiac arrest (COSCA) in adults should include survival, neurological function, and health-related quality of life. This should be reported as survival status and modified Rankin scale score at hospital discharge, at 30 days, or both. Health-related quality of life should be measured with ≥ 1 tools from Health Utilities Index version 3, Short-Form 36-Item Health Survey, and EuroQol 5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow. © 2018 European Resuscitation Council and American Heart Association, Inc. Published by Elsevier B.V. All rights reserved.

Introduction

Sudden cardiac arrest is one of the leading causes of death in industrialised nations. In the United States, $\approx 360\,000$ cardiac arrests are attended by emergency services each year, with only 10.6% of patients surviving to hospital discharge [1]. Similar statistics apply across Europe and all other industrialised areas worldwide [2,3]. However, survival rates vary widely both globally [4] and regionally [5,6], with 4-fold or more regional variations reported. These low and variable survival rates highlight the importance of research that seeks to improve patient outcomes.

Randomised trials are important tools for evaluating the clinical efficacy and cost-effectiveness of interventions for in- and out-of-hospital cardiac arrest. Two broad types of trials have been

described—efficacy and effectiveness. Efficacy (sometimes called *explanatory*) trials aim to test whether an intervention works under optimal situations. Effectiveness (sometimes called *pragmatic*) trials are designed to assess how well an intervention works in routine clinical practice [7]. Ordinarily, efficacy trials focus on assessing the impact of an intervention on a short-term outcome that is well correlated with long-term prognosis. Effectiveness trials seek to provide evidence of the longer-term health impact of an intervention [8,9]. Evaluated outcomes can include clinical, clinician-reported, and patient-reported outcomes and resource use or economic impact. Clinical trials provide essential evidence of the relative benefit of an intervention for stakeholders as diverse as clinicians, patients, and policy makers. Outcome selection is, therefore, an important aspect of trial design [9,10].

Sometimes multiple trials might evaluate the same intervention in

[☆] This article has been copublished in *Circulation: Cardiovascular Quality and Outcomes*.

¹ Drs Haywood and Whitehead contributed equally to this article.

Fig. 1. OMERACT framework 2.0 modified for cardiac arrest. ICU indicates intensive care unit; OMERACT, Outcome Measures in Rheumatology; QOL, quality of life; and ROSC, return of spontaneous circulation. Reprinted from Boers et al. [18] Copyright © 2014, The Authors. <https://creativecommons.org/licenses/by-nc-nd/3.0/>.

different settings. Reconciling disparate trial results can be challenging if each trial evaluated different outcomes at different time points. A systematic review of cardiac arrest trials published between 2000 and 2012 included 61 publications that identified > 160 different trial outcomes [11]. No single outcome was reported across all trials. The majority of outcomes reflected short-term clinical and clinician-reported outcomes, focusing on pathophysiological manifestations and process-based measures. Although survival was the most commonly reported outcome, 39 different definitions of survival were used. Patient-reported outcomes [12] were rarely reported, although more recent trials have included these outcomes [13,14]. This suggests that essential evidence of the impact of care from the survivors' perspective is currently missing from clinical trials.

Adopting a consistent approach to outcome reporting for effectiveness trials has the potential to reduce heterogeneity in reporting, improve transparency in outcome selection, reduce reporting bias, and increase information available to pool for meta-analysis. Standardised reporting frameworks have been developed for reporting the findings of observational studies drawn from resuscitation registries [15,16]. These frameworks recommend 23 core data elements and 30 supplementary elements across the 5 domains of system, dispatch, patient, process, and outcome [17]. International guidelines exist for core outcomes to use in effectiveness trials in patients with other conditions [18]. Becker et al. [19] considered choices of primary outcomes across a range of resuscitation science studies but concluded that no single primary outcome was appropriate for all studies of cardiac arrest; however, no international guidelines exist to define a focused core outcome set (COS) for use in effectiveness trials in patients with cardiac arrest.

The COMET initiative (Core Outcome Measures for Effectiveness Trials) promotes the development and application of agreed standardised sets of outcomes known as COS [20]. A COS is defined as a small, standardised group of outcomes that should be measured and reported, as a minimum, in all effectiveness trials for a specific health area [20,21]. Effectiveness trials should aim to capture the COS as part of their a priori-defined primary or secondary outcomes.

The COSCA initiative (Core Outcome Set for Cardiac Arrest), in collaboration with the International Liaison Committee on Resuscitation (ILCOR), sought to develop a COS for cardiac arrest effectiveness trials covering both in- and out-of-hospital cardiac arrest. This consensus article draws on the views and experiences of patients,

the public, clinicians, policy makers, researchers, and the international perspectives represented through the ILCOR collaborative network. The process was informed by systematic reviews of the literature, as well as qualitative research involving cardiac arrest survivors. A total of 168 participants used a Delphi process to draft a core cardiac arrest outcome set, and a 2-day meeting was convened to develop consensus recommendations.

Methods

The available evidence associated with the development of COS [18,20] and the websites of key COS development groups (COMET and OMERACT [Outcome Measures in Rheumatoid Arthritis Clinical Trials], later renamed Outcome Measures in Rheumatology) informed our approach. The project was registered with the COMET initiative [22]. Ethical approval was obtained from the National Health Service Black Country Research Ethics Committee (13/W/0464) to enable patients and their partners to participate.

Development of a COS involved 2 key steps: development of a core domain set (ie, what to measure) followed by identification of appropriate measurement tools (ie, how to measure) [18,20]. A *core domain set* was defined as referring to the minimum number of health domains (outcomes or aspects of health) that must be assessed. That is, it specifies what should be measured. Importantly, this stage was driven by what is important and not how an outcome is assessed. The second stage involved the establishment of a core outcome measurement set, that is, the specific methods of assessment (ie, how to measure) for the domains identified in step 1. The selection of measurement tools was informed by an appraisal of measurement quality, relevance, and feasibility.

The OMERACT initiative suggests that a COS should seek to include at least 1 health domain across each of 4 core areas of health (Fig. 1): 3 core areas consider the impact of a health condition (ie, survival, life impact, economic impact/resource use), and the fourth core area reflects any pathophysiological manifestations associated with the condition [18]. Several reviews [11,23,24] suggest that these domains are relevant and encompass the large number of outcomes assessed in cardiac arrest trials.

To develop the consensus outcome criteria, a 4-stage approach was used, which consisted of the following steps, each of which is explained

in detail: (1) stage 1: generation of an extensive list of potential outcomes across 4 core areas of health; (2) stage 2: an international Delphi approach to refine and prioritise a list of potential outcomes; (3) stage 3: an international expert panel meeting; and (4) stage 4: synthesis of findings and recommendations for measurement tools.

Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas of Health

This stage was informed by a systematic review of the literature and qualitative interviews with cardiac arrest survivors and their partners. The systematic review focused on the identification of outcomes reported from randomised controlled trials that enrolled adults who had sustained a cardiac arrest [11]. The findings from the systematic review were supplemented by conducting semistructured interviews with adult cardiac arrest survivors (and, if available, their partners) between 3 and 12 months after discharge from the hospital after their cardiac arrest. Interviews were conducted, recorded, and transcribed with NVivo (QSR International, London, United Kingdom) by Dr Whitehead. Data were analysed using interpretative phenomenological analysis, which seeks to capture the individual's experience of a phenomenon and how they understand their experiences [25]. Findings from the systematic review and qualitative research were synthesised to produce an extensive list of potential outcomes. These were grouped under the OMERACT core area headings of survival, life impact, resource use/economic, and pathophysiological manifestations of cardiac arrest for consideration in stage 2.

Stage 2: International Delphi Approach to Refine and Prioritise List of Potential Outcomes

The list of potential outcomes identified during stage 1 were placed into an online survey tool (SurveyMonkey, Dublin, Ireland). Separate surveys were developed for healthcare professionals and patients/patient advocates. The ILCOR network of 7 regional resuscitation councils was used to solicit the views of healthcare professionals and patient and public advocates. Each ILCOR member ($n=27$) was asked to invite 6 healthcare professionals and 3 patients to participate in the relevant surveys by E-mail. The outcomes were prioritised in 2 rounds. Questions were structured to allow participants to rate the importance of each outcome at 5 different time points across the patient journey: during cardiopulmonary resuscitation (CPR), immediately after CPR, during hospitalisation, at hospital discharge, and within the first year after the cardiac arrest. In the first round, survey participants were also given the opportunity to suggest additional outcomes they considered important if they were not currently included in the survey. At the end of each round, outcomes rated as being of critical importance by $> 70\%$ of respondents and rated as being of limited importance by $< 15\%$ of respondents were advanced for additional consideration by the expert panel in stage 3. Similarly, those outcomes rated of limited importance by $> 70\%$ of respondents and of critical importance by $< 15\%$ of respondents were discarded. The findings from the first round were summarised and presented for a second round of prioritisation. Any new suggestions were included in the second round. The second round of prioritisation differed by asking participants to rank outcomes according to importance. Outcomes that received strong support ($> 70\%$ agreement) were also advanced for consideration by the expert panel in stage 3. Outcomes that received moderate support (60%–69% agreement) were also presented to the expert panel in stage 3.

Stage 3: International Expert Panel Meeting

The aim of the international expert panel was to consider the shortlist of outcomes identified during stage 2 and select a COS comprising 4 to 8 outcomes and make recommendations of measurement

tools to capture those outcomes. A 2-day consensus meeting was convened in Prague, Czech Republic, in October 2015. A group of experts uninformed in previous stages was purposefully selected to capture those involved in clinical research (clinicians, clinical trialists, methodologists), experts in the use of measurement tools for cardiac arrest, healthcare providers involved in treating patients with cardiac arrest (physicians, nurses, paramedics, allied health professionals), and survivors of cardiac arrests and patient advocates.

Before the meeting, the participants were sent a written summary of the outcome selection process described above. At the start of the meeting, an overview of steps undertaken and findings from stages 1 and 2 were presented. The shortlisted outcomes were presented in a matrix that covered the OMERACT core area headings of survival, life impact, resource use/economic, and pathophysiological manifestations of cardiac arrest during CPR, immediately after CPR, during hospitalisation, at hospital discharge, and within the first year after the cardiac arrest. Initial presentations were followed by semistructured, small-group discussions that covered the 4 core areas. Each core area was assigned a facilitator who supported 4 rounds of discussions on that topic. Each discussion group included a survivor of cardiac arrest or a patient advocate, as well as several researchers and clinicians who participated in small-group discussion across each core area. Each group nominated a recorder. The groups were tasked to consider the importance, relevance, acceptability, and feasibility of the short-listed outcomes as potential core outcomes for cardiac arrest effectiveness trials. The facilitator encouraged all group members to participate in discussions and shared key findings from each group with the next. This enabled consideration of and building upon what other participants had discussed, facilitated the identification of issues of agreement and disagreement, and supported a flow of new ideas or key issues between groups. Thereafter, participants reconvened in a whole-group discussion session, in which facilitators and group recorders summarised feedback from the small-group discussions, including areas of agreement and disagreement. The large-group discussion sought to collectively explore agreement and refine issues or concerns raised within each core area. At the end of the first day, expert panel members were invited to reflect on the day's discussions and then vote for up to 7 outcomes they believed should be included as core outcomes. Secure electronic votes were submitted by use of TurningPoint software and ResponseWare keypads (Turning Technologies, Youngstown, Ohio). The second day followed a similar model of large- and small-group discussions designed to allow further discussion and reflection on the optimal outcomes. A second round of voting was used to identify the final list of core outcomes. Proceedings were captured in the form of detailed written records from discussion groups, plenary sessions, and the outcome of voting.

Stage 4: Synthesis of Findings and Recommendations for Measurement Tools

A writing group was appointed by ILCOR and endorsed by the American Heart Association Manuscript Oversight Committee after review for conflicts of interest. The charge to the group was to draw together and summarise the findings from stages 1 through 3. The group met by teleconference on 8 occasions and face-to-face on 1 occasion.

The writing group reviewed and summarised the findings from stages 1 through 3 presented in this scientific statement. The group undertook further work with the intention of making recommendations on relevant measurement tools for the outcome domains selected in stage 3. This was informed by considering existing measurement tools in cardiac arrest and other relevant diseases or injuries and discussing their quality, acceptability, and feasibility for application in clinical trials. Final recommendations were reached through discussion and consensus among the writing group members.

Results

Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas (OMERACT Framework)

The systematic review identified 61 randomised trials that reported 164 unique outcomes on 278 occasions [11]. The most frequently reported outcome was survival (85% of trials). This included return of spontaneous circulation (ROSC) before hospital admission, in the emergency department, or at any point during the resuscitation attempt. Survival was reported at various time points from emergency department admission, hospital discharge, and through to 3 years. There was a lack of consistency in definition and the time points at which survival was assessed, although most studies (90%) reported survival up to and including hospital discharge. Pathophysiological outcomes (e.g., coronary perfusion pressure, arterial blood gas results) and life impact were frequently reported, although there was a lack of consistency in outcomes, measurement tools, and the timings of assessments. Process of care (e.g., event timings), response to treatment (e.g., temperature achieved in targeted temperature management trials), quality of CPR, intervention success rates (e.g., vascular access), and adverse outcomes were reported in a quarter of studies. Writing group members identified trials published more recently that reported outcomes in the domain of life impact [13,14,26,27].

Eleven interviews (8 patients, 3 partners) were conducted to provide a detailed understanding of the lived experience of those surviving cardiac arrest. Five key themes were identified by patients that reflected the disruption to normality caused by cardiac arrest (survival, physical activities, emotional well-being, social well-being, and the impact on others; Table 1).

The findings from the systematic review and patient/partner interviews were used to produce an extensive list of 53 potential outcomes, encompassing survival (5), life impact (24), economic impact and resource use (10), and pathophysiological manifestations (14), which were used in the stage 2 Delphi process.

Table 1

Themes From Patient and Partner Interviews Relating to Disruption to Normality

Theme	Examples
Survival	Closeness to death Gratitude to be alive
Impairment and impact on activities	Fatigue Breathlessness Vision Muscle weakness Pain (e.g., fractured ribs) Activities of daily living/increased dependence
Emotional well-being	Cognitive function Anxiety Confidence Depression Self-esteem Personality changes Frustration
Social well-being and participation	Participation (role: job, voluntary, career) Participation (leisure: hobbies, sports) Participation (social activities) Participation (family: relationships, intimacy)
Impact on others	Increased work/care Impact to participation—hobbies, work Strain on relationships Worry

Core Area	Outcome Domain	Timing of Measurement				
		During CPR	Immediately after CPR	During hospital stay	At hospital discharge	Within 1 year
Pathophysiological manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurologic markers)		○	○▲		
	Adverse events					▲
	CPR process measures*					
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health-related quality of life				○	●▲
	Emotional wellbeing					▲
	Family impact					▲
	Participation				△	●▲
Economic impact and resource use	Fatigue					▲
	Cost-effectiveness					
	Hospital-free survival*					

Fig. 2. Outcome domains presented for discussion at COSCA meeting. Circles indicate healthcare professionals and researchers; triangles indicate patients and partners. Grey fill indicates strong consensus (< 70%); white fill indicates moderate support. Grey boxes were not rated or ranked on their importance. COSCA indicates Core Outcome Set for Cardiac Arrest; and CPR, cardiopulmonary resuscitation. *Hospital-free survival and CPR process measures were introduced during expert panel meeting.

Stage 2: International Delphi Approach to Refine and Prioritise Long List of Potential Outcomes

Ninety-nine healthcare professionals, 62 cardiac arrest survivors, and 7 relatives of cardiac arrest victims from 15 countries participated in the Delphi survey. The clinician group included 48 physicians, 12 nurses, 21 allied health professionals, 6 academics and 12 others. By the end of the 2 Delphi rounds, 25 outcome domains were prioritised (Fig. 2).

Stage 3: International Expert Panel Meeting

A total of 23 expert panel members (including 2 survivors, 1 partner, and 1 patient advocate) participated from 11 countries (United Kingdom, the Netherlands, Finland, Germany, Belgium, Sweden, United States, Canada, Singapore, Australia, and New Zealand). The core outcome discussions and recommendations are summarised below.

Pathophysiological Manifestations

The expert panel considered circulatory function, respiratory

function, and brain function as potential core outcomes. There was general agreement that the assessment of these outcomes is of high importance during and immediately after cardiac arrest. They become less important once ROSC has been achieved. Consideration was given to the potential for pathophysiological measures to act as surrogate assessments for longer-term functional outcomes. For example, specific neuroimaging/electrophysiological tests might be a useful surrogate to reflect the impact of a cardiac arrest on brain function [28]. The panel considered these outcomes might be valuable during the validation of new interventions and advancing discovery, for example, in efficacy trials; however, there was general agreement that the assessment of specific pathophysiological manifestations as core outcomes across the wide range of effectiveness trials in this field is of limited value.

The importance of reporting adverse events was discussed at length. There was general agreement that the reporting of adverse events should occur in accordance with Good Clinical Practice guidelines, which are relevant to all clinical trials, rather than as a core outcome specific for cardiac arrest.

Although not introduced during the Delphi survey, participants discussed the importance of the quality of CPR (ie, CPR process) and its potential use as a core outcome. Such measures could include compression rate, preshock pause duration, compression depth, or time to intervention. There was unanimous consensus that the processes of CPR are important contributors to outcome after cardiac arrest. Participants recognised that CPR can be initiated or completed before a study intervention is applied. Although CPR process could be an indicator of the quality of a resuscitation system of care or a potential modifier of the effect of a study intervention, it was concluded that CPR process should not be a core outcome for effectiveness trials. This should not limit researchers from reporting CPR quality matrices to enable the assessment of associations between CPR performance and COS categories. Where such data are reported, use of standardised definitions [29] and time intervals could reduce variation in reporting [30].

Survival

The expert panel discussed the relative importance of short-term survival, such as ROSC. The outcome was thought to be important in efficacy studies, which seek to advance discovery in this field, but contributed less toward understanding the longer-term aspects of survival.

Hospital-free survival (number of days alive and permanently outside a hospital in the first 30 days after cardiac arrest) was introduced during discussions. It was recently used in a large, pragmatic cardiac arrest trial [31] and offers potential statistical efficiencies over dichotomous outcomes [32,33]. Challenges can exist around the interpretation of a composite outcome, which combines survival with length of hospital stay.

The panel concluded that longer-term survival (alive/dead) should be the core survival outcome.

Life Impact

Patient/partner participants voiced a number of potentially overlapping domains that can be affected after a cardiac arrest, which included cognition and consciousness, physical symptoms, activities of daily living, health-related quality of life (HRQoL), emotional well-being, family impact, participation, and fatigue. It was agreed that among the most common and significant impacts of cardiac arrest are potential changes to cognition and neurological functioning. Other contributors to daily life, such as physical, social, and emotional changes after returning home, were discussed and considered important. To capture these important domains of health, a multidomain approach, including assessing an individual's HRQoL after arrest, was

favoured.

The panel reached consensus that neurological function and HRQoL should be included as core outcomes.

Economic Evaluation

Although domains reflective of this core area were not prioritized by participants in the Delphi survey, the importance attributed to this core area in the OMERACT initiative suggested that further discussion of the relative importance of this core area and possible domains was required. Group discussion highlighted the complexities of capturing sufficient information to allow for a full economic analysis of costs related to cardiac arrest. Although economic evaluation was judged to be important, it was agreed that there was insufficient evidence to inform categorisation currently. As a result, economic measures were not suggested as a core outcome.

Stage 4: Recommendations for Measurement Tools and Timing of Measurement

Survival

Survival to discharge and survival to 30 days were considered to be better indicators of patient recovery than shorter-term survival, such as survival to admission or 4 to 6 hours after emergency department arrival. Discussion highlighted international variation in the feasibility of collecting information on survival at discharge and survival at 30 days. Both time points have limitations: survival to discharge is limited by cultural differences (whether patients are discharged home to die or die predominantly in the hospital) and health system differences (efficiency of discharge processes; whether long-term care is provided in the hospital or in home care settings). This can limit comparisons across different health systems. Survival to specific intervals (e.g., 30 days) after arrest can avoid some of these limitations but in some settings requires consent, which, as noted elsewhere, can introduce bias through higher rates of loss to follow-up.

The writing group concluded that neither time point is perfect, and for consistency with the Utstein recommendations [17], it was agreed either survival to hospital discharge or survival to 30 days would be acceptable to report as core outcomes. Researchers are encouraged to report both measures if feasible but should avoid reporting these as a composite outcome (survival to discharge or survival to 30 days) because this impairs pooling results in a meta-analysis.

Neurological Function

Five clinician-completed measures—the Cerebral Performance Category (CPC) [34], Structured CPC (assessment by semistructured interview) [35], CPC-Extended [36], Glasgow Outcome Scale–Extended [37], and modified Rankin Scale (mRS) [38]—were considered. Moderate associations between the tools suggest that they measure related but not identical constructs [13,35,39–42]. The CPC was not highly endorsed because of the lack of discrimination between scores and the potential for ceiling effects and overestimation of function [14,43–46]. The CPC-Extended was considered to show good evidence of content validity, reliability, acceptability, and feasibility, although its use in cardiac arrest survivors was limited at this time [36]. The mRS and Glasgow Outcome Scale–Extended appear to provide improved granularity [41,43]. The mRS has been used more extensively in cardiac arrest survivors [13,41,47–55] than the Glasgow Outcome Scale–Extended [44,56] or CPC-Extended [37].

The writing group reached unanimous agreement that the mRS should be the outcome measurement tool of choice for neurological function. The mRS is a brief, clinician-completed, ordinal hierarchical rating scale used to determine a summary score of global disability

Table 2
Core Outcomes, Time Point, and Preferred Methods for Collection

Outcome	Time Point	Preferred Method	Alternative Method
Survival	30 d or discharge	Ambulance/hospital records Death registry	
Neurological function (mRS)	30 d or discharge	Face-to-face interview by trained raters using mRS-9Q	Informant interview Telephone assessment Review of hospital records
Quality of life	90 d	Face-to-face (proxy completion where respondents are unable to participate)	Telephone interviews Postal questionnaire

mRS indicates modified Rankin Scale; and mRS-9Q, 9-question mRS.

[57,58] after a neurological event or condition. The mRS captures impairment of physical and cognitive abilities. Questions primarily focus on limitations in basic, instrumental, and more advanced daily activities and restrictions in ability to participate in normal social roles [58,59]. There is evidence that it can discriminate between levels of mild and moderate disability [58]. It does not, however, provide detailed information of residual impairments and is unable to differentiate between whether effects are attributable to neurological or other sources of disability [58,60].

How to Complete

mRS completion is preferably measured by direct interview with the patient and any relevant caregiver, either face-to-face or by telephone (Table 2) [57]. Nonstandardised interview administration requires ≈5 minutes [57]. When patients are unable to participate in interviews because of physical, language, or cognitive impairment, proxy completion—that is, completion by informants, such as family members, caregivers, or health professionals who know the patient well—can be considered. However, proxy completion without the involvement of the patient is associated with suboptimal levels of reliability and validity [57,61]. Although some studies suggest that indirect mRS completion from hospital records is less accurate [62], others suggest acceptable reliability after chart review by trained health professionals [36,39].

Substantial inter-rater reliability of the mRS has been described [63] although this can be improved through digital training [63], use of a structured interview [59,64], or use of a web-based tool with 9 questions (mRS-9Q) and an mRS calculator [65]. Use of trained raters and a structured approach to calculating the mRS score is recommended. Raters should also be familiar with problems common after cardiac arrest.

Timing

The advantages and disadvantages outlined above for reporting survival status at discharge or at 30 days apply similarly to the reporting of favourable neurological function. Additional limitations of measuring neurological function at discharge are that the patient will not have been exposed to normal/their previous activities to allow accurate determination of the relevant mRS category. The time of discharge is also likely to be influenced by the degree and speed of recovery, with those having the greatest disabilities remaining in the hospital longer. Additional challenges imposed by assessing neurological function at 30 days include the requirement for the research team to specifically follow up with the patient, because unlike mortality, these data often are not tracked routinely. Incomplete follow-up confers a risk of introducing attrition bias. Whichever time point is selected, the outcome should be reported as measured on the day of the assessment and not the best ever achieved.

The writing group accepted that there were advantages and disadvantages to both time points, and similar to our suggestion for assessing survival status, mRS score at discharge or 30 days was

considered acceptable for reporting as a core outcome. Researchers can report both time points if feasible but should avoid reporting as a composite outcome (mRS score at discharge or 30 days) because this impairs pooling results in a meta-analysis.

What to Report

Historically, cardiac arrest trials have dichotomised neurological outcomes into favourable or unfavourable categories based on an mRS cutoff of ≤ 3 [17,66,67]. However, in stroke trials, an mRS score of ≤ 1 [68] or ≤ 2 [69] has been used to represent the cut off between favourable and unfavourable outcomes.

To enable consistent reporting and comparisons between articles, the writing group advised that the core outcome be presented as the number and percentage of patients in each of the 6 categories rather than solely being categorised into favourable and unfavourable neurological outcome groups. This approach also provides greater granularity on clinically-relevant outcomes [70].

To facilitate the transition to mRS as the core outcome measurement tool and to support backward comparability, the writing group was also supportive of continued reporting of the CPC score over the next 5 years, in addition to the mRS score. Useful information for calculating the mRS score can be found on the Internet [71].

The COSCA writing group suggested the use of the mRS version, where category 4 (moderate severe disability) includes dependency to attend to own bodily needs as separate from ability to walk unassisted (*or* instead of *and*). Outcome after cardiac arrest is less influenced by locomotor problems than after stroke, and this version will be more sensitive in identifying extensive dependency related to severe cognitive impairment in a patient still able to walk. This version is available online [71]. The scoring is as follows: 0 = no symptoms; 1 = no significant disability—able to carry out all usual activities, despite some symptoms; 2 = slight disability—able to look after own affairs without assistance but unable to carry out all previous activities; 3 = moderate disability—requires some help but able to walk unassisted; 4 = moderately severe disability—unable to attend to own bodily needs without assistance and/or unable to walk unassisted; 5 = severe disability—requires constant nursing care and attention, bedridden, incontinent; and 6 = dead.

Health-Related Quality of Life

The writing group spent considerable time deliberating which tools should be used to capture HRQoL after cardiac arrest. Key considerations were the relevance or acceptability to cardiac arrest survivors, feasibility (e.g., ease of use, information collection methods), the measurement properties and their previous use in the cardiac arrest patient population, and cost. The writing group prioritised 6 generic measures of HRQoL for detailed consideration: 2 multi-item profile measures (the Short-Form 36-Item Health Survey [SF-36] [72] and Short-Form 12-Item Health Survey [SF-12] [73,74]) and 4 preference-based, multiattribute utility measures (the 15-dimension Quality of Life

Table 3
Summary and Item Content of Short-listed Generic HRQoL Measures (n = 3)

PROM Details, Developer, Website, Cost (License), Completion Time	Conceptual Focus, Response Options/Recall Period, Completion Format, Language Versions	HRQoL Domains [80] (Number of Items Per Domain)		How to Score		
		Symptom Status: Symptoms		Functional Status		General Health Perception
		Physical	Cognitive	Psychological	Social/ Role	
Preferences based (2)						
HUI3 Website: www.healthutilities.com License for use per project; minimum fee \$3000 (US) Completion time: ≈ 8 min for self-completion; ≈ 3 min for interview completion (not reported in cardiac arrest population) User guide: Available once HUI3 is purchased Country of origin: Canada	Preference-based, comprehensive system for measuring health status and HRQoL and for producing utility scores. Applicable for all people aged ≥ 5 y. HUI3 classification system: describes the comprehensive health state of an individual across 8 attributes of general health (6 of 8 items reflect physical functional status) Response options: Between 4 and 6 descriptive response options (ability/disability) Recall period: “Current” or “Usual”; “Usual” recommended for clinical studies. Choice of 1-, 2-, or 4-wk recall available Completion: Self, interview (in person; telephone), or proxy (proxy version available) supported Language: 16 versions, including English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Russian, Spanish, Swedish	Pain-severity (1) Ambulation: Ability to walk (distances) Dexterity: Ability to use hands and fingers Senses: Vision Senses: Hearing Speech: Ability to be understood (5)	Cognition: ability to solve day-to-day problems (1)	Emotion: happiness and interest in life (1)	Usual activities (including work, study, housework, and family or leisure activities) (1)	2 ways of presenting data: 1. HUI3 utility index: scored using single-attribute and multi-attribute utility functions HUI-specific coding algorithms to support calculation of single-attribute Utility Score (Index) Index range –0.36 to 1.00, where 1.00 is perfect health, 0 is dead, and < 0 is a health state worse than death Population-based norms available 2. Multiattribute descriptive system (“Classification system”) reflects individual item scores
EuroQoL EQ-5D-5L (EQ-5D-5L) Website: https://www.euroqol.org/ License: For use per project; free, but use must be registered on EuroQoL website [81] Completion time: < 5 min (not reported in cardiac arrest population) User guide: Free on website [82] Country of origin: Multiple	Standardised, preference-based measure of health status for use in clinical and economic appraisal EQ-5D descriptive system: 5 items across “5 domains” (2 of 5 reflect physical functional status) (EQ VAS: self-rated health on a 20-cm vertical visual analogue scale) Response options: 5-level categorical response options per item (no problems [1] to extreme problems [5]) Completion of all items will produce a 5-digit number describing the respondent’s health state (but the numerals 1–5 have no inherent arithmetic properties and should not be used as a cardinal score) Recall period: Today Completion: Self, interview (in person, telephone), or proxy (2 proxy versions) supported [83] Formats: PDA, pen and paper, proxy paper, tablet, telephone, web [83] Language: > 120 language versions: See website	Pain/discomfort (1) Mobility Self-care (2)	–	Anxiety/depression (1)		

Table 3 (continued)

PROM Details, Developer, Website, Cost (License), Completion Time	Conceptual Focus, Response Options/Recall Period, Completion Format, Language Versions	HRQoL Domains [80] (Number of Items Per Domain)		How to Score			
		Symptom Status: Symptoms	Functional Status			General Health Perception	
			Physical	Cognitive	Psychological		
Profile measures (1)							
Short Form 36-Item Health Survey, version 2 (SF-36v2) Website: https://campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html License: For use per project; minimum fee \$US Survey license request: via website Completion time: Range 5–30 min (not reported in cardiac arrest population) User guide: Available once SF-36v2 is purchased Country of origin: United States	Functional health and well-being from the patient's perspective: underpinned by 8 health domains across both physical (4) and mental (4) aspects of health Total 35 items plus 1 health transition item Response options: Between 3- and 6-level categorical response options per item Recall period: Standard recall 4 wk; acute recall 1 wk Completion: Self, interview (in person; telephone), or proxy supported Language: > 170 language versions: See website The IQOLA project supported the development of conceptually equivalent and culturally appropriate translations [84] Note: utility values A preference-based utility index, the SF-6D, can be calculated after completion of the SF-36 to inform economic analyses [85]	Bodily pain (2) Vitality: fatigue/tiredness (2)	Physical functioning (10) Role limitation (4)	-	Mental health (5) Role limitation (3)	Social functioning (2)	2 ways of presenting the data: 2.1 Eight-domain profile 2.2 Two component summary scales: PCS, MCS Scoring requires SF-36-specific algorithm. Norm-based scoring: score transformed to 0–100 (mean 50 [SD 10]) Population-based norms available

EQ VAS indicates EuroQol visual analogue scale; HRQoL, health-related quality of life; HUI3, Health Utilities Index 3; IQOLA, International Quality of Life Assessment; MCS, mental component summary; PCS, physical component summary; PDA, personal digital assistant; and PROM, patient-reported outcome measure.

questionnaire [15-D] [75], the Health Utilities Index version 3 [HUI3] [76], and both the original and revised versions of the EuroQol [EQ-5D-3L [77] and EQ-5D-5L [78], respectively]. All preference-based measures include both descriptive systems and a utility index and hence could be used in cost-utility evaluations [79].

The group was unable to reach consensus and recommend a single tool among these measures. Patient and public partners highlighted that none of the tools comprehensively captured their experiences of the aftermath of a cardiac arrest. In online voting, the HUI3, followed by the SF-36 and EQ-5D-5L, received the most support (Table 3). The briefest measures are the EQ-5D-5L (5 items) and HUI3 (8 items); the longest is the SF-36v2 (36 items). Although all measures are intended to be measures of health status or HRQoL, the number of items and HRQoL coverage vary (Table 3). The HUI3 and EQ-5D-5L have a preponderance of items that relate to physical health, whereas items within the SF-36v2 are equally distributed between physical and mental health [79]. Only the HUI3 includes items that measure cognition, speech, and dexterity, which are concerns relevant to cardiac arrest survivors. Only the SF-36v2 includes an assessment of fatigue.

Preference-based utility scores can be calculated for HUI3, EQ-5D-5L, and SF-36v2 (in the form of the SF-6D [86]), which supports their use in cost-utility evaluation. The SF-36v2 provides the most detailed profile score; that is, separate scores are calculated across the 8 health domains, providing a more detailed assessment of health status than is otherwise afforded by the 2 summary scores. More limited descriptive profile scores can also be reported for both the HUI3 and EQ-5D across their 8 and 5 attributes, respectively. Normative population data are available for all measures, which supports data interpretation and between-group comparisons. Estimates of meaningful change have been calculated for all measures after completion by the general population and specific patient groups, which further supports data interpretation. License requests are required for all measures, but only the EQ-5D-5L is free to use.

A review of published evidence on the reliability and validity of these measures after completion by survivors of cardiac arrest demonstrated that the strongest evidence was available for the HUI3, followed by the SF-36v2 [87]. The EQ-5D-5L has not been evaluated in this population; however, evaluations in comparable populations suggest improved data quality and psychometric performance compared with the original EQ-5D-3L [78].

In summary, multiple measures of HRQoL, including the SF-36v2, EQ-5D-5L, and HUI3, are acceptable for measurement of outcomes in trials enrolling patients with cardiac arrest. Each of these has strengths and weaknesses compared with other measures available. HUI3 has been applied frequently to patients with cardiac arrest and directly measures cognition. The other measures are also acceptable.

How to Complete

Although all of the HRQoL measures discussed here were developed to be self-completed, all have been successfully administered by interview in person [40,42], via the telephone [13,56,88,89], or both [14] in the cardiac arrest population. Postal self-completion, although possible, has been used infrequently. However, the ability to self-complete a questionnaire after a cardiac arrest can be severely impaired by cognitive impairment (which can result in an overestimation of ability) [90], fatigue, or general poor health. Although proxy ratings of non-observable constructs such as emotional well-being and cognition can underestimate limitations [91,92], agreement is generally greater for more physical attributes [91,93,94]. Cronberg et al. [14] described interview-based proxy completion of the SF-36v2 with 8% of survivors at 6-month follow-up. Where possible, proxy completion by

appropriate, well-informed assessors is suggested to ensure that the views of survivors who are unable to self-report are included in trials and the results do not underestimate the impact of cardiac arrest on HRQoL [94].

Timing

There was consensus that HRQoL should be measured after the patient's discharge from the hospital. Patient recovery often continues to 6 months and beyond. Three-quarters of patients of a working age return to work after cardiac arrest at a median interval of 4 months [95]. The optimal time points and frequency of follow-up need to be considered in the context of study resources and overall study design. If sufficient resources are available to measure postdischarge outcomes, the group recommends, as a minimum, assessment at 90 days. The group considered that this best balanced the trade-off between costs and other implications associated with longer-term follow-up with the positive effect of the value and stability of the data and is consistent with the review of primary outcomes by Becker et al. [19]. However, it is recognised that health status can continue to change in the subsequent months and that capturing this change is important [41,95,96]. Therefore, the group agreed that HRQoL could also be assessed at 180 days or 1 year, or both. However, the longer duration of follow-up would be associated with increased logistic challenges and could be influenced by factors external to surviving a cardiac arrest.

Discussion

The COSCA writing group identified that survival, neurological function, and HRQoL should be reported as core outcomes in cardiac arrest effectiveness trials. Survival status should be reported at hospital discharge, at 30 days, or both. Neurological function (measured with the mRS) should be reported at hospital discharge, 30 days, or both. HRQoL should be measured with ≥ 1 tools from the HUI3, SF-36v2, or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

COS are intended to enhance standardisation of outcomes that are reported for effectiveness trials. As such, future cardiac arrest effectiveness trials should include the core outcomes identified by COSCA as part of the *a priori*-designated primary or secondary trial outcomes. The COS are intended to be complementary to other outcome measures relevant to the particular intervention under evaluation. The COS recommendations sit alongside, rather than replace, tools designed to enhance the quality and transparency of health research, such as SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [97] and CONSORT (Consolidated Standards of Reporting Trials) [98] (Fig. 3). Earlier phase trials will typically focus primarily on measures of efficacy, such as biomarkers, ROSC, or immediate survival, although selected core outcomes could also be considered.

Traditionally, outcome assessment of patients experiencing cardiac arrest has focused on survival rates and clinician-based assessments of outcome [11]. However, the growth in patient-centred care and recognition of the importance of seeking to understand the impact of cardiac arrest from the perspective of the survivor demand a shift in the way that outcomes (in particular, over the longer term) are assessed in clinical trials. The use of well-developed questionnaires, which provide an assessment of how patients feel, function, and live their lives because of their health and health care, can provide essential patient-derived information to enhance outcome reporting in clinical trials [99]. Such questionnaires or patient-reported outcome measures can be simply categorised as generic or specific (to a condition [e.g., diabetes mellitus], a problem [e.g., cognition], a function [e.g., activities of daily

Fig. 3. Core outcome sets as part of Good Clinical Practice. Clinical trials are conducted within the overall framework of Good Clinical Practice, which supports clear and transparent reporting. Core outcome sets are suggested for inclusion as part of the a priori-designated primary or secondary end points of effectiveness trials. They enhance the quality and transparency of health research promoted by SPIRIT and CONSORT. CONSORT indicates Consolidated Standards of Reporting Trials; EQ-5D-5L, 5-level EQ-5D; HUI3, Health Utilities Index version 3; mRS, modified Rankin scale; QoL, quality of life; SF-36, 36-item Short Form Survey; and SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

life], or a population [e.g., children]).

Generic measure of HRQoL, such as those short-listed in the COSCA recommendations (HUI3, SF-36v2, EQ-5D-5L), includes multi-dimensional concepts (physical, social, emotional, and mental functioning) that provide a general assessment of HRQoL of relevance to patients and the general population, facilitating between-group comparisons and ensuring that the patient perspective is captured in clinical trials. Although the generic measures supported by COSCA start to move the focus toward patient-centred outcomes, the current tools still fail to comprehensively capture the breadth of outcomes and experiences that matter most to cardiac arrest survivors [100–102]. As a consequence, the impact of cardiac arrest and associated health care might be incompletely assessed. Although a condition-specific measure for survivors of cardiac arrest does not currently exist, measures specific to problems of relevance to cardiac arrest survivors (e.g., cognition, fatigue, anxiety, social participation) are available and have been used increasingly in this population [13,14,26,27,103–105]. Although the COSCA recommendations do not currently include guidance for ≥ 1 problems or function-specific measures, per good practice guidance for outcome assessment [91,92], where possible, we encourage their inclusion. Although not yet evaluated in the cardiac arrest population, the PROMIS initiative (Patient Reported Outcome Measures Information System [106]) describes a range of fixed or dynamic (computer adaptive tests) self-report measures of physical, mental, and social health appropriate for use with the general population and those with chronic conditions and hence suitable for comparing the burden of illness and treatment impact. The paucity of evidence to suggest which tools are best suited highlights the need for further research in this area.

Collecting HRQoL measures as an outcome of a clinical trial can be challenging and expensive. Sometimes, such data are missing from patients with the poorest outcomes, which can result in systematic bias, which cannot be ignored [107,108]. To maximise the quality and timeliness of quality-of-life measures and reduce the risk of systematic bias caused by missing data, standardised administration and routine

screening for avoidable missing data are advised [108–110]. The approaches used and handling of missing data should be detailed in the study protocol and standard operating procedures [107,109].

The writing group was cognisant of the balance that needs to be struck between the requirements of collecting the core outcomes identified by the COSCA initiative at a time of constrained research resources and the need to accelerate the pace of evidence-based change in resuscitation practices. The overall efficiency of the research pathway can be improved through a better understanding of the pathophysiology and effects of therapeutic interventions from animal and laboratory studies. By establishing proof of concept with evidence from early efficacy trials, internal pilot studies could reduce redundancy in effectiveness trials [111–113]. Improving the efficiency of the conduction of trials [114] and making use of registry data, where possible [115], could reduce costs and shorten the time to complete trials. The use of fixed dichotomous analysis of ordered categorical outcomes is rarely the most statistically efficient approach and usually requires a larger sample size to demonstrate efficacy than other approaches [68]. Alternative analytical approaches such as shift analysis and ordinal logistic regression, used widely in stroke research [68,70], require further evaluation in the cardiac arrest population. A better understanding of measurement properties of continuous outcomes, such as hospital-free survival [32], might also aid reductions in sample size and trial costs.

Conclusions

Through a partnership between patients, partners, clinicians, and researchers and endorsed by ILCOR, consensus emerged that a COS for reporting on effectiveness studies of cardiac arrest (COSCA) should include survival, neurological function, and HRQoL. To facilitate meaningful comparisons across studies over time, survival status and mRS at hospital discharge, 30 days, or both should be reported. HRQoL should be measured with ≥ 1 tools from the HUI3, SF-36v2, or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

Disclosures

<i>Writing Group Disclosures</i>								
Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Vinay M. Nadkarni	Children's Hospital Philadelphia	None	None	None	None	None	None	None
Gavin D. Perkins	Warwick Medical School and Heart of England NHS Foundation Trust (United Kingdom)	National Institute for Health Research (Research funding to support research in cardiac arrest including PARAMEDIC2) [†]	None	None	None	None	None	None
Felix Achana	Clinical Trials Unit, University of Warwick Medical School (United Kingdom)	None	None	None	None	None	None	None
Stefanie Beesems	Academic Medical Center (Netherlands)	Physio-Control (the ARREST database is maintained by an unconditional grant of Physio-Control Inc, Redmond, WA) [†]	None	None	None	None	None	None
Bernd W. Böttiger	Cologne Department of Anesthesiology (Germany)	None	ERC Director Science & Research, GRC Chairman, Board Member DIVI, member of Advisory Board of the DIVI Foundation; member of the Scientific Committee*	Med update GmbH, FomF GmbH, Baxalta Deutschland GmbH, Bayer Vital GmbH, Boehringer Ingelheim, ZOLL Medical Deutschland GmbH, Bard GmbH [†]	None	None	None	None
Anne Brooks	None	None	None	None	None	None	None	None
Maaret Castrén	Helsinki University Hospital (Finland)	None	None	None	None	None	None	None
Kirstie Haywood	Warwick Research in Nursing, Warwick Medical School, Warwick University (United Kingdom)	None	None	None	None	None	None	None
Mary Fran Hazinski	Vanderbilt University School of Nursing	None	None	None	None	None	Consultant, Senior Science Editor, AHA Emergency Cardiovascular Care [†]	None

Rudolph W. Koster	Academic Medical Center (Netherlands)	Physio-Control [†]	None	None	None	None	HeartSine [*] ; Physio-Control (unpaid) [*]	None
Gisela Lilja	Lund University, Skane University Hospital, Sweden Center for Cardiac Arrest (Sweden)	Steering group member in the Target Temperature Management trial 2 (Noncommercial multicentre trial expected to include the first patient in September 2017) [*]	None	None	None	None	None	None
John Long	National Police Staff College (United Kingdom)	None	None	None	None	None	None	None
Koenraad G. Monsieurs	Antwerp University Hospital (Belgium)	None	None	None	None	None	None	None
Peter T. Morley	University of Melbourne Clinical School, Royal Melbourne Hospital (Australia)	None	None	None	None	None	None	None
Laurie Morrison	Rescu, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto (Canada)	Heart and Stroke Foundation of Canada [†] ; CIHR (operating grants in sepsis and opioid-related cardiac arrest and operating grant in OHCA) [‡] ; CanNET (program grant on OHCA) [†]	None	None	None	None	None	Robert and Dorothy Pitts Chair in Acute Care and Emergency Medicine [†]
Graham Nichol	University of Washington-Harborview Center for Prehospital Emergency Care	ZOLL Medical Corp, Chelmsford, MA (grant to UW in support of Dynamic AED Registry) [*] ; FDA, Silver Spring, MD (grant to UW in support of Dynamic AED Registry) [*] ; Sotera Wireless Inc, San Diego, CA (grant to UW in support of PHAROS Network) [*] ; NIH (grant to UW in support of co-PI, Resuscitation Outcomes Consortium Coordinating Center) [†]	None	None	None	None	ZOLL Circulation, San Jose, CA [*]	None
Marcus EH Ong	Singapore General Hospital and Duke-NUS Graduate Medical School (Singapore)	ZOLL Medical Corp (PI) [*] ; Laerdal Medical (PI) [†]	None	None	None	None	Global Healthcare (unpaid) [*]	None

Valentino Oriolo	Bristol Heart Institute (United Kingdom)	NIHR (PhD Clinical Fellowship)*	None	Astra Zeneca*; Bristol-Myers Squibb*	None	None	None	None
Gustavo Saposnik	St. Michael's Hospital, University of Toronto (Canada)	None	None	None	None	None	None	Heart and Stroke Foundation of Canada (Dr Saposnik is supported by the HSFC Career Scientist Award after an open peer-reviewed competition) [†]
Michael Smyth	University of Warwick (United Kingdom)	None	None	None	None	None	None	None
Ken Spearpoint	University of Hertfordshire (United Kingdom)	(NIHR funded) Paramedic 2 trial (PI multicentre RCT of adrenaline vs placebo in out-of-hospital cardiac arrest)*; Patients Experiences of Recovery from Cardiac Arrest (PI for qualitative research study pertinent to his doctoral studies; sponsored by University of Hertfordshire and does not require any funding)*	None	None	None	None	None	None
Laura Whitehead	University of Warwick, Warwick Medical School (United Kingdom)	None	None	None	None	None	None	None
Barry Williams	None	None	None	None	None	None	None	None

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Steve A. Aguilar	Kaiser Permanente	None	None	None	None	None	None	None
Steven M. Bradley	Minneapolis Heart Institute	None	None	None	None	None	None	None
Tomas Drabek	University of Pittsburgh	None	None	None	None	None	None	None
Rohan Khera	UT Southwestern Medical Center	None	None	None	None	None	None	None

Acknowledgments

This scientific statement is dedicated to the memory of Dr Ian Jacobs, who inspired, supported, and contributed to the COSCA initiative. Dr Jacobs was a lifelong volunteer of the Australian Resuscitation Council and co-chair of ILCOR at the time of his death. His legacy and contributions to the science of resuscitation and compassionate cardiac arrest care will live on through COSCA's focus on patient-centred outcomes.

The authors acknowledge the support and guidance from ILCOR and its member councils, including the American Heart Association, European Resuscitation Council, Heart and Stroke Foundation of Canada, Australia and New Zealand Committee on Resuscitation, Resuscitation Council of Southern Africa, Inter-American Heart Foundation, and Resuscitation Council of Asia. The authors thank the COSCA Collaborators for their contributions to this document: Richard Aickin, Kristofer Årstedt, Jonathan Bengert, Steve Brett, Allan de Caen, Raffo Escalante, Judith Finn, Karl Kern, Swee Han Lim, Jerry P. Nolan, Jasmeet Soar, Tzong-Luen Wang, and Kathy Williams. ILCOR is grateful for the dedication and support of Eileen M. Censullo, MBA, RRT; Amber Rodriguez PhD; and the AHA Emergency Cardiovascular Care Staff.

References

- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JHY, Alger HM, Wong SS, Muntner P, on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–603. <http://dx.doi.org/10.1161/CIR.0000000000000485>.
- Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, Baubin M, Mols P, Hadžibegović I, Ioannides M, Škulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdóttir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Strömsöe A, Burkart R, Perkins GD, Bossaert LL, EuReCa ONE, Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation*. 2016;105:188–95. <http://dx.doi.org/10.1016/j.resuscitation.2016.06.004>.
- Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, Sarah AK, Ng YY, Li WY, Ma MH. PAROS Clinical Research Network, Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2015;96:100–8. <http://dx.doi.org/10.1016/j.resuscitation.2015.07.026>.
- Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation*. 2010;81:1479–87. <http://dx.doi.org/10.1016/j.resuscitation.2010.06.008>.
- Perkins GD, Cooke MW. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emerg Med J*. 2012;29:3–5. <http://dx.doi.org/10.1136/emmermed-2011-200758>.
- Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423–31. <http://dx.doi.org/10.1001/jama.300.12.1423>.
- Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis*. 1967;20:637–48.
- Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, Lam M, Seguin R. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol*. 2003;3:28. <http://dx.doi.org/10.1186/1471-2288-3-28>.
- Macefield RC, Avery KN, Blazeby JM. Integration of clinical and patient-reported outcomes in surgical oncology. *Br J Surg*. 2013;100:28–37. <http://dx.doi.org/10.1002/bjs.8989>.
- Stanley K. Design of randomized controlled trials. *Circulation*. 2007;115:1164–9. <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.594945>.
- Whitehead L, Perkins GD, Clarey A, Haywood KL. A systematic review of the outcomes reported in cardiac arrest clinical trials: the need for a core outcome set. *Resuscitation*. 2015;88:150–7. <http://dx.doi.org/10.1016/j.resuscitation.2014.11.013>.
- Aufderheide TP, Pirralo RG, Provo TA, Lurie KG. Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest. *Crit Care Med*. 2005;33:734–40.
- Nichol G, Guffey D, Stiell IG, Leroux B, Cheskes S, Idris A, Kudenchuk PJ, Macphee RS, Wittwer L, Rittenberger JC, Rea TD, Sheehan K, Rac VE, Raina K, Gorman K, Aufderheide T. Resuscitation Outcomes Consortium Investigators. Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: a ROC PRIMED substudy. *Resuscitation*. 2015;93:74–81. <http://dx.doi.org/10.1016/j.resuscitation.2015.05.011>.
- Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Åneman A, Ståmmet P, Erlinge D, Friberg H, Hassager C, Kuiper M, Wanscher M, Bosch F, Cranshaw J, Kleger GR, Persson S, Undén J, Walden A, Winkel P, Wetterslev J, Nielsen N. TTM Trial Investigators. Neurologic function and health-related quality of life in patients following targeted temperature management at 33 °C vs 36 °C after out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA Neurol*. 2015;72:634–41. <http://dx.doi.org/10.1001/jamaneurol.2015.0169>.
- Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, Bossaert L, Deloos HH, Dick WF, Eisenberg MS, Evans TR, Holmberg S, Kerber R, Mullie A, Ornato JP, Sandoe E, Skulberg A, Tunstall-Pedoe H, Swanson R, Thies WH. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style: a statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991;84:960–75.
- Jacobs I, Nadkarni V, the ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation. Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–97. <http://dx.doi.org/10.1161/01.CIR.0000147236.85306.15>.
- Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Grasser JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Ma MH, McNally BF, Morley PT, Morrison JL, Monsieurs KG, Montgomery W, Nichol G, Okada K, Ong ME, Travers AH, Nolan JP, for the Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation. *Circulation*. 2015;131:1286–300. <http://dx.doi.org/10.1161/CIR.0000000000000144>.
- Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, Conaghan PG, Bingham III CO, Brooks P, Landewé R, March L, Simon LS, Singh JA, Strand V, Tugwell P. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol*. 2014;67:745–53. <http://dx.doi.org/10.1016/j.jclinepi.2013.11.013>.
- Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT, Halperin HR, on behalf of the American Heart Association Emergency Cardiovascular Care Committee. Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. *Circulation*. 2011;124:2158–77. <http://dx.doi.org/10.1161/CIR.0b013e3182340239>.
- Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132. <http://dx.doi.org/10.1186/1745-6215-13-132>.
- Gargon E, Gurgun B, Medley N, Altman DG, Blazeby JM, Clarke M, Williamson PR. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One*. 2014;9:e99111. <http://dx.doi.org/10.1371/journal.pone.0099111>.
- The development of a core outcome set for cardiac arrest clinical trials. COMET Initiative website (Core Outcome Measures in Effectiveness Trials). <http://www.comet-initiative.org/studies/details/284>. Accessed January 7, 2017.
- Elliott VJ, Rodgers DL, Brett SJ. Systematic review of quality of life and other patient-centred outcomes after cardiac arrest survival. *Resuscitation*. 2011;82:247–56. <http://dx.doi.org/10.1016/j.resuscitation.2010.10.030>.
- Trzeciak S, Jones AE, Kilgannon JH, Fuller BM, Roberts BW, Parrillo JE, Farrar JT. Outcome measures utilized in clinical trials of interventions for postcardiac arrest syndrome: a systematic review. *Resuscitation*. 2009;80:617–23. <http://dx.doi.org/10.1016/j.resuscitation.2009.03.014>.
- Smith JA, Flowers P, Larkin M. Interpretative Phenomenological Analysis: Theory, Method and Research. London, England: Sage Publications; 2009.
- Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, Kuiper M, Martini A, Mellingshoff J, Pelosi P, Wanscher M, Wise MP, Östman I, Cronberg T. Anxiety and depression among out-of-hospital cardiac arrest survivors. *Resuscitation*. 2015;97:68–75. <http://dx.doi.org/10.1016/j.resuscitation.2015.09.389>.
- Tiainen M, Poutiainen E, Oksanen T, Kaukonen KM, Pettilä V, Skrifvars M, Varpula T, Castrén M. Functional outcome, cognition and quality of life after out-of-hospital cardiac arrest and therapeutic hypothermia: data from a randomized controlled trial. *Scand J Trauma Resusc Emerg Med*. 2015;23:12. <http://dx.doi.org/10.1186/>

- s13049-014-0084-9.
- 28 Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO, Soar J. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation*. 2014;85:1779–89. <http://dx.doi.org/10.1016/j.resuscitation.2014.08.011>.
 - 29 Kramer-Johansen J, Edelson DP, Losert H, Köhler K, Abella BS. Uniform reporting of measured quality of cardiopulmonary resuscitation (CPR). *Resuscitation*. 2007;74:406–17. <http://dx.doi.org/10.1016/j.resuscitation.2007.01.024>.
 - 30 Talikowska M, Tohira H, Bailey P, Finn J. Cardiopulmonary resuscitation quality: widespread variation in data intervals used for analysis. *Resuscitation*. 2016;102:25–8. <http://dx.doi.org/10.1016/j.resuscitation.2016.02.008>.
 - 31 Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, Stiell I, Morrison LJ, Aufderheide TP, Cheskis S, Christenson J, Kudenchuk P, Vaillancourt C, Rea TD, Idris AH, Colella R, Isaacs M, Straight R, Stephens S, Richardson J, Conde J, Schmicker RH, Egan D, May S, Ornato JP, for the ROC, Investigators. Trial of continuous or interrupted chest compressions during CPR. *N Engl J Med*. 2015;373:2203–14. <http://dx.doi.org/10.1056/NEJMoa1509139>.
 - 32 Nichol G, Brown SP, Perkins GD, Kim F, Sterz F, Broeckel Elrod JA, Mentzelopoulos S, Lyon R, Arabi Y, Castrén M, Larsen P, Valenzuela T, Graesner JT, Youngquist S, Khunkhlay N, Wang HE, Ondrej F, Sastrias JM, Barasa A, Sayre MR. What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey. *Resuscitation*. 2016;107:115–20. <http://dx.doi.org/10.1016/j.resuscitation.2016.08.004>.
 - 33 Morton SE, Chiew YS, Pretty C, Moltchanova E, Scarrott C, Redmond D, Shaw GM, Chase JG. Effective sample size estimation for a mechanical ventilation trial through Monte-Carlo simulation: length of mechanical ventilation and ventilator free days. *Math Biosci*. 2017;284:21–31. <http://dx.doi.org/10.1016/j.mbs.2016.06.001>.
 - 34 Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P, BRCIT Study Group. Assessment of neurological prognosis in comatose survivors of cardiac arrest. *Lancet*. 1994;343:1055–9. [http://dx.doi.org/10.1016/S0140-6736\(94\)90179-1](http://dx.doi.org/10.1016/S0140-6736(94)90179-1).
 - 35 Mak M, Moulart VR, Pijls RW, Verbunt JA. Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category. *Resuscitation*. 2016;100:6–10. <http://dx.doi.org/10.1016/j.resuscitation.2015.12.005>.
 - 36 Balouris SA, Raina KD, Rittenberger JC, Callaway CW, Rogers JC, Holm MB. Development and validation of the Cerebral Performance Categories- Extended (CPC-E). *Resuscitation*. 2015;94:98–105. <http://dx.doi.org/10.1016/j.resuscitation.2015.05.013>.
 - 37 Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15:573–85. <http://dx.doi.org/10.1089/neu.1998.15.573>.
 - 38 Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044–54.
 - 39 Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation*. 2011;82:1036–40.
 - 40 Raina KD, Callaway C, Rittenberger JC, Holm MB. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*. 2008;79:249–56. <http://dx.doi.org/10.1016/j.resuscitation.2008.06.005>.
 - 41 Raina KD, Rittenberger JC, Holm MB, Callaway CW. Functional outcomes: one year after a cardiac arrest. *Biomed Res Int*. 2015;2015:283608. <http://dx.doi.org/10.1155/2015/283608>.
 - 42 Stiell IG, Nesbitt LP, Nichol G, Maloney J, Dreyer J, Beaudoin T, Blackburn J, Wells GA. OPALS Study Group. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emerg Med*. 2009;53:241–8. <http://dx.doi.org/10.1016/j.annemergmed.2008.03.018>.
 - 43 Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammel P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, for the TTM Trial Investigators. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. *N Engl J Med*. 2013;369:2197–206. <http://dx.doi.org/10.1056/NEJMoa1310519>.
 - 44 Deasy C, Bray J, Smith K, Harriss L, Bernard S, Cameron P, for the VACAR Steering Committee. Functional outcomes and quality of life of young adults who survive out-of-hospital cardiac arrest. *Emerg Med J*. 2013;30:532–7.
 - 45 Arrich J, Zeiner A, Sterz F, Janata A, Uray T, Richling N, Behringer W, Herkner H. Factors associated with a change in functional outcome between one month and six months after cardiac arrest: a retrospective cohort study. *Resuscitation*. 2009;80:876–80. <http://dx.doi.org/10.1016/j.resuscitation.2009.04.045>.
 - 46 Stiell I, Nichol G, Wells G, De Maio V, Nesbitt L, Blackburn J, Spaite D, for the OPALS Study Group. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation*. 2003;108:1939–44. <http://dx.doi.org/10.1161/01.CIR.0000095028.95929.B0>.
 - 47 Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association between duration of resuscitation and favorable outcome after out-of-hospital cardiac arrest: implications for prolonging or terminating resuscitation. *Circulation*. 2016;134:2084–94. <http://dx.doi.org/10.1161/CIRCULATIONAHA.116.023309>.
 - 48 Winther-Jensen M, Kjaergaard J, Wanscher M, Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Friberg H, Gasche Y, Horn J, Hovdenes J, Kuiper M, Pellis T, Stammel P, Wise MP, Åneman A, Hassager C. No difference in mortality between men and women after out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:78–84. <http://dx.doi.org/10.1016/j.resuscitation.030201506>.
 - 49 Iqbal MB, Al-Hussaini A, Rosser G, Salehi S, Phylactou M, Rajakulasingham R, Patel J, Elliott K, Mohan P, Green R, Whitbread M, Smith R, Ilsey C. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield Cardiac Arrest Study). *Am J Cardiol*. 2015;115:730–7. <http://dx.doi.org/10.1016/j.amjcard.2014.12.033>.
 - 50 Maynard C, Longstreth Jr. WT, Nichol G, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlborn D, Deem S, Olsufka M, Cobb LA, Kim F. Effect of prehospital induction of mild hypothermia on 3-month neurological status and 1-year survival among adults with cardiac arrest: long-term follow-up of a randomized, clinical trial. *J Am Heart Assoc*. 2015;4:e001693. <http://dx.doi.org/10.1161/JAHA.114.001693>.
 - 51 Winther-Jensen M, Pellis T, Kuiper M, Koopmans M, Hassager C, Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Friberg H, Gasche Y, Horn J, Hovdenes J, Stammel P, Wanscher M, Wise MP, Åneman A, Kjaergaard J. Mortality and neurological outcome in the elderly after target temperature management for out-of-hospital cardiac arrest. *Resuscitation*. 2015;91:92–8. <http://dx.doi.org/10.1016/j.resuscitation.2014.12.030>.
 - 52 Cheskis S, Common MR, Byers AP, Zhan C, Silver A, Morrison LJ. The association between chest compression release velocity and outcomes from out-of-hospital cardiac arrest. *Resuscitation*. 2015;86:38–43. <http://dx.doi.org/10.1016/j.resuscitation.2014.10.020>.
 - 53 Greer DM, Scripko PD, Wu O, Edlow BL, Bartscher J, Sims JR, Camargo EE, Singhal AB, Furie KL. Hippocampal magnetic resonance imaging abnormalities in cardiac arrest are associated with poor outcome. *J Stroke Cerebrovasc Dis*. 2013;22:899–905. <http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2012.08.006>.
 - 54 Beesems SG, Wittebrood KM, de Haan RJ, Koster RW. Cognitive function and quality of life after successful resuscitation from cardiac arrest. *Resuscitation*. 2014;85:1269–74. <http://dx.doi.org/10.1016/j.resuscitation.2014.05.027>.
 - 55 Nielsen N, Winkel P, Cronberg T, Erlinge D, Friberg H, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammel P, Wanscher M, Wise MP, Åneman A, Wetterslev J. Detailed statistical analysis plan for the target temperature management after out-of-hospital cardiac arrest trial. *Trials*. 2013;14:300. <http://dx.doi.org/10.1186/1745-6215-14-300>.
 - 56 Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. *Circulation*. 2015;131:174–81. <http://dx.doi.org/10.1161/CIRCULATIONAHA.114.011200>.
 - 57 Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging*. 2013;8:201–11. <http://dx.doi.org/10.2147/CIA.S32405>.
 - 58 Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38:1091–6. <http://dx.doi.org/10.1161/01.STR.0000258355.23810.c6>.
 - 59 Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke*. 2005;36:777–81. <http://dx.doi.org/10.1161/01.STR.0000157596.13234.95>.
 - 60 Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5:603–12. [http://dx.doi.org/10.1016/S1474-4422\(06\)70495-1](http://dx.doi.org/10.1016/S1474-4422(06)70495-1).
 - 61 McArthur K, Beagan ML, Degnan A, Howarth RC, Mitchell KA, McQuaig FB, Shannon MA, Stott DJ, Quinn TJ. Properties of proxy-derived modified Rankin Scale assessment. *Int J Stroke*. 2013;8:403–7. <http://dx.doi.org/10.1111/j.1747-4949.2011.00759.x>.
 - 62 Quinn TJ, Ray G, Atula S, Walters MR, Dawson J, Lees KR. Deriving modified Rankin scores from medical case-records. *Stroke*. 2008;39:3421–3. <http://dx.doi.org/10.1161/STROKEAHA.108.519306>.
 - 63 Quinn TJ, Lees KR, Hardemark HG, Dawson J, Walters MR. Initial experience of a digital training resource for modified Rankin scale assessment in clinical trials. *Stroke*. 2007;38:2257–61. <http://dx.doi.org/10.1161/STROKEAHA.106.480723>.
 - 64 Wilson JT, Hareendran A, Grant M, Baird T, Schulz UG, Muir KW, Bone I. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke*. 2002;33:2243–6.
 - 65 Patel N, Rao VA, Heilman-Espinoza ER, Lai R, Quesada RA, Flint AC. Simple and reliable determination of the modified Rankin Scale score in neurosurgical and neurological patients: the mRS-9Q. *Neurosurgery*. 2012;71:971–5. <http://dx.doi.org/10.1227/NEU.0b013e318268a56>.
 - 66 Stiell IG, Nichol G, Leroux BG, Rea TD, Ornato JP, Powell J, Christenson J, Callaway CW, Kudenchuk PJ, Aufderheide TP, Idris AH, Daya MR, Wang HE, Morrison LJ, Davis D, Andrusiek D, Stephens S, Cheskis S, Schmicker RH, Fowler R, Vaillancourt C, Hostler D, Zive D, Pirrallo RG, Vilke GM, Sopko G, Weisfeldt M, for the ROC, Investigators. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:787–97. <http://dx.doi.org/10.1056/NEJMoa1010076>.
 - 67 Aufderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, Kudenchuk PJ, Christenson J, Daya MR, Dorian P, Callaway CW, Idris AH, Andrusiek D, Stephens SW, Hostler D, Davis DP, Dunford JV, Pirrallo RG, Stiell IG, Clement CM, Craig A, Van Ottingham L, Schmidt TA, Wang HE, Weisfeldt ML, Ornato JP, Sopko G, for the

- Resuscitation Outcomes Consortium (ROC) Investigators. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:798–806. <http://dx.doi.org/10.1056/NEJMoa1010821>.
- 68 Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, Howard G, Saver JL, on behalf of the European Stroke Organisation Outcomes Working Group. Statistical analysis of the primary outcome in acute stroke trials [published correction appears in *Stroke*. 2012; 43:e100]. *Stroke* 2012;43:1171–8. <http://dx.doi.org/10.1161/STROKEAHA.111.641456>.
 - 69 Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. *Stroke*. 2007;38:3055–62. <http://dx.doi.org/10.1161/STROKEAHA.107.488536>.
 - 70 Lees KR, Bath PM, Schellinger PD, Kerr DM, Fulton R, Hacke W, Matchar D, Sehra R, Toni D, for the European Stroke Organization Outcomes Working Group. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. *Stroke*. 2012;43:1163–70. <http://dx.doi.org/10.1161/STROKEAHA.111.641423>.
 - 71 Modified Rankin Scale calculator. <http://www.modifiedrankin.com>. Accessed January 7, 2017.
 - 72 Ware JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36) I: conceptual framework and item selection. *Med Care*. 1992;30:473–83.
 - 73 Ware Jr. J, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–33.
 - 74 Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. 1999;53:46–50.
 - 75 Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med*. 2001;33:328–36.
 - 76 Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, Denton M, Boyle M. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. *Med Care*. 2002;40:113–28.
 - 77 The EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.
 - 78 Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–36. <http://dx.doi.org/10.1007/s11136-011-9903-x>.
 - 79 Richardson J, Khan MA, Iezzi A, Maxwell A. Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI 3, 15D, QWB, and AQL-8D multiattribute utility instruments. *Med Decis Making*. 2015;35:276–91.
 - 80 Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual model of health-related quality of life. *J Nurs Scholarsh*. 2005;37:336–42.
 - 81 EQ-5D registration form. EuroQol website. <http://www.euroqol.org/registration-form>. Accessed January 7, 2017.
 - 82 EQ-5D user guides. EuroQol website. <https://euroqol.org/publications/user-guides/>. Accessed January 7, 2017.
 - 83 EQ-5D-5L available modes of administration. EuroQol website. <https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/>. Accessed January 7, 2017.
 - 84 International Quality of Life Assessment website. www.iqola.org. Accessed January 7, 2017.
 - 85 Measuring and valuing health: SF-6D. University of Sheffield website. <https://www.sheffield.ac.uk/scharr/sections/heds/mvh/sf-6d>. Accessed January 7, 2017.
 - 86 Brazier J, Czoski-Murray C, Roberts J, Brown M, Symonds T, Kelleher C. Estimation of a preference-based index from a condition-specific measure: the King's Health Questionnaire. *Med Decis Making*. 2008;28:113–26. <http://dx.doi.org/10.1177/0272989X07301820>.
 - 87 Haywood KL, Pearson N, Morrison LJ, Castrén M, Lilja G, Perkins GD. Assessing health-related quality of life (HRQoL) in survivors of out-of-hospital cardiac arrest: a systematic review of patient-reported outcome measures. *Resuscitation*. 2018;123:22–37.
 - 88 Longstreth Jr. WT, Nichol G, Van Ottingham L, Hallstrom AP. Two simple questions to assess neurologic outcomes at 3 months after out-of-hospital cardiac arrest: experience from the public access defibrillation trial. *Resuscitation*. 2010;81:530–3. <http://dx.doi.org/10.1016/j.resuscitation.2010.01.011>.
 - 89 Andrew E, Nehme Z, Bernard S, Smith K. Comparison of health-related quality of life and functional recovery measurement tools in out-of-hospital cardiac arrest survivors. *Resuscitation*. 2016;107:57–64. <http://dx.doi.org/10.1016/j.resuscitation.2016.07.242>.
 - 90 Pusswald G, Fertl E, Faltl M, Auff E. Neurological rehabilitation of severely disabled cardiac arrest survivors, part II: life situation of patients and families after treatment. *Resuscitation*. 2000;47:241–8.
 - 91 Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke*. 2004;35:607–12. <http://dx.doi.org/10.1161/01.STR.0000110984.91157.BD>.
 - 92 Irwin DE, Gross HE, Stucky BD, Thissen D, DeWitt EM, Lai JS, Amtmann D, Khashtou L, Varni JW, DeWalt DA. Development of six PROMIS pediatrics proxy-report item banks. *Health Qual Life Outcomes*. 2012;10:22. <http://dx.doi.org/10.1186/1477-7525-10-22>.
 - 93 Rogers J, Ridley S, Chrispin P, Scotton H, Lloyd D. Reliability of the next of kins' estimates of critically ill patients' quality of life. *Anaesthesia*. 1997;52:1137–43.
 - 94 Sneeuw KC, Aaronson NK, Sprangers MA, Detmar SB, Wever LD, Schornagel JH. Value of caregiver ratings in evaluating the quality of life of patients with cancer. *J Clin Oncol*. 1997;15:1206–17. <http://dx.doi.org/10.1200/JCO.1997.15.3.1206>.
 - 95 Kragholm K, Wissenberg M, Mortensen RN, Fonager K, Jensen SE, Rajan S, Lippert FK, Christensen EF, Hansen PA, Lang-Jensen T, Hendriksen OM, Kober L, Gislason G, Torp-Pedersen C, Rasmussen BS. Return to work in out-of-hospital cardiac arrest survivors: a nationwide register-based follow-up study. *Circulation*. 2015;131:1682–90. <http://dx.doi.org/10.1161/CIRCULATIONAHA.114.011366>.
 - 96 Larsson IM, Wallin E, Rubertsson S, Kristofferzon ML. Health-related quality of life improves during the first six months after cardiac arrest and hypothermia treatment. *Resuscitation*. 2014;85:215–20. <http://dx.doi.org/10.1016/j.resuscitation.2013.09.017>.
 - 97 Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
 - 98 Schulz KF, Altman DG, Moher D, the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials*. 2010;11:32. <http://dx.doi.org/10.1186/1745-6215-11-32>.
 - 99 Haywood K, Brett J, Salek S, Marlett N, Penman C, Shklarov S, Norris C, Santana MJ, Stanisewska S. Patient and public engagement in health-related quality of life and patient-reported outcomes research: what is important and why should we care? Findings from the first ISOQOL patient engagement symposium. *Qual Life Res*. 2015;24:1069–76. <http://dx.doi.org/10.1007/s11136-014-0796-3>.
 - 100 Haywood KL, Brett J, Tutton E, Stanisewska S. Patient-reported outcome measures in older people with hip fracture: a systematic review of quality and acceptability. *Qual Life Res*. 2017;26:799–812. <http://dx.doi.org/10.1007/s11136-016-1424-1>.
 - 101 Pietersma S, de Vries M, van den Akker-van Marle ME. Domains of quality of life: results of a three-stage Delphi consensus procedure among patients, family of patients, clinicians, scientists and the general public. *Qual Life Res*. 2014;23:1543–56. <http://dx.doi.org/10.1007/s11136-013-0578-3>.
 - 102 Kuspinar A, Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics*. 2014;32:759–73. <http://dx.doi.org/10.1007/s40273-014-0167-5>.
 - 103 Moulart VR, van Heugten CM, Winkens B, Bakx WG, de Krom MC, Gorgels TP, Wade DT, Verbunt JA. Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: a randomised controlled trial. *Int J Cardiol*. 2015;193:8–16. <http://dx.doi.org/10.1016/j.ijcard.2015.04.229>.
 - 104 Perkins GD, Woollard M, Cooke MW, Deakin C, Horton J, Lall R, Lamb SE, McCabe C, Quinn T, Slowther A, Gates S, PARAMEDIC Trial Collaborators. Prehospital randomised assessment of a mechanical compression device in cardiac arrest (PARAMEDIC) trial protocol. *Scand J Trauma Resusc Emerg Med*. 2010;18:58. <http://dx.doi.org/10.1186/1757-7241-18-58>.
 - 105 Lilja G, Nielsen N, Friberg H, Horn J, Kjaergaard J, Nilsson F, Pellis T, Wetterslev J, Wise MP, Bosch F, Bro-Jeppesen J, Brunetti I, Buratti AF, Hassager C, Hofgren C, Insoori A, Kuiper M, Martini A, Palmer N, Rundgren M, Rylander C, van der Veen A, Wanscher M, Watkins H, Cronberg T. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33 °C versus 36 °C. *Circulation*. 2015;131:1340–9. <http://dx.doi.org/10.1161/CIRCULATIONAHA.114.014414>.
 - 106 Intro to PROMIS. HealthMeasures website. <http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis>. Accessed January 7, 2017.
 - 107 Fairclough DL, Peterson HF, Chang V. Why are missing quality of life data a problem in clinical trials of cancer therapy? *Stat Med*. 1998;17:667–77.
 - 108 Bernhard J, Cella DF, Coates AS, Fallowfield L, Ganz PA, Moinpour CM, Mosconi P, Osoba D, Simes J, Hürny C. Missing quality of life data in cancer clinical trials: serious problems and challenges. *Stat Med*. 1998;17:517–32.
 - 109 Kyte D, Reeve BB, Efficace F, Haywood K, Mercieca-Bebber R, King MT, Norquist JM, Lenderking WR, Snyder C, Ring L, Velikova G, Calvert M. International Society for Quality of Life Research commentary on the draft European Medicines Agency reflection paper on the use of patient-reported outcome (PRO) measures in oncology studies. *Qual Life Res*. 2016;25:359–62. <http://dx.doi.org/10.1007/s11136-015-1099-z>.
 - 110 Bhardwaj A, Rehman SU, Mohammed AA, Gaggini HK, Barajas L, Barajas J, Moore SA, Sullivan D, Januzzi JL. Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *Am Heart J*. 2012;164. <http://dx.doi.org/10.1016/j.ahj.2012.08.015>. 793-799.e1.
 - 111 Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, Williams H, Blazeby JM. members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research, Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open*. 2017;7:e013537. <http://dx.doi.org/10.1136/bmjopen-2016-013537>.
 - 112 Bugge C, Williams B, Hagen S, Logan J, Glazener C, Pringle S, Sinclair L. A process for Decision-making after Pilot and feasibility Trials (ADEPT): development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials*. 2013;14:353. <http://dx.doi.org/10.1186/1745-6215-14-353>.
 - 113 Luce BR, Connor JT, Broglio KR, Mullins CD, Ishak KJ, Saunders E, Davis BR. on behalf of the RE-ADAPT (REsearch in ADaptive methods for Pragmatic Trials) Investigators, Using Bayesian adaptive trial designs for comparative effectiveness

- research: a virtual trial execution. *Ann Intern Med.* 2016;165:431–8. <http://dx.doi.org/10.7326/M15-0823>.
- 114 Treweek S, Altman DG, Bower P, Campbell M, Chalmers I, Cotton S, Craig P, Crosby D, Davidson P, Devane D, Duley L, Dunn J, Elbourne D, Farrell B, Gamble C, Gillies K, Hood K, Lang T, Littleford R, Loudon K, McDonald A, McPherson G, Nelson A, Norrie J, Ramsay C, Sandercock P, Shanahan DR, Summerskill W, Sydes M, Williamson P, Clarke M. Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform. *Trials.* 2015;16:261. <http://dx.doi.org/10.1186/s13063-015-0776-0>.
- 115 Li G, Sajobi TT, Menon BK, Korngut L, Lowerison M, James M, Wilton SB, Williamson T, Gill S, Drogos LL, Smith EE, Vohra S, Hill MD, Thabane L. on behalf of 2016 Symposium on Registry-Based Randomized Controlled Trials in Calgary, Registry-based randomized controlled trials: what are the advantages, challenges, and areas for future research? *J Clin Epidemiol.* 2016;80:16–24. <http://dx.doi.org/10.1016/j.jclinepi.2016.08.003>.